CURRICULLUM VITAE – Eric Maimon

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Date& place of birth:13.12.1963, Beer-Sheva, Israel

Army service: 02.02.1982-27.01.1985 (paramedic)

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• **Education**:

1986-1989: B.Sc. in Chemistry at Ben-Gurion University of the Negev, Beer-Sheva, Israel

1989-1992: M.Sc. in Chemistry at Ben-Gurion University of the Negev, Beer-Sheva, Israel. **Supervisor:** Prof. Dany Kost. **Thesis subject:** The chiral S-N axis Sulfanamide.

1997-2002: Ph.D. in chemistry at Ben-Gurion Univ. of the Negev, Beer-Sheva, Israel. **Supervisors:** Prof. Dan Meyerstein and Prof. Haim Cohen
Thesis subject: Chemical properties of transition metal complexes with macrocyclic and linear tertiary polyamine ligands.

• **Employment**:

2011-present: Head of Radiation Chemistry group, Chemistry dept., NRCN
2010-2011: Visiting Senior researcher at the *Dept. of Material Science and Eng., Univ. of Maryland, USA*(sabbatical)
1997-2010: Head of the Analytical Laboratory, NRCN
1995-1997: Manager of Development & Research, Chemada Industries.
1992-1995: Manager of Analytical Laboratory, Luxemburg Industries.

• **Organizing roles in International Conferences**:

1. Organizer of the 28th Miller Conference on Radiation Chemistry, Dead Sea, Israel, **2013**

• **Memberships/Fellowships**

1. Israeli Analytical Chemical Society
2. Israel Chemical Society
3. Israeli Society for Research of Radicals and Oxygen species
4. American Chemical Society

• **Educational Activities:**

(a) Research Students:

Towards Ph.D. degree in Chemistry at Ben Gurion University of the Negev:

1. Dr. Yael Albo (co-supervisor Prof. Dan Meyerstein) – graduated 2008
2. Dr. Yair Lavi (co-supervisor Prof. Dan Meyerstein) – graduated 2009
3. Dr. Lioubov (Luba) Kats (co-supervisor Prof. Dan Meyerstein) – graduated 2011
4. Dr. Guy Yardeni (co-supervisors Prof. Dan Meyerstein) – graduated 2012
5. Dr. Inna Popivker (advisor. Supervisors - Prof. Dan Meyerstein and Dr. Israel Zilbermann) – graduated 2013

Towards M.Sc. degree in Chemistry at Ben Gurion University of the Negev:

1. Mrs. Nina Buzaglo (co-supervisor Prof. Dan Meyerstein) – graduated 2011
2. Ms. SmadarAttia (co-supervisor Prof. Dan Meyerstein) – graduated 2013
3. Mrs. Lena Mikhailovich-Jivin (co-supervisors Prof. Dan Meyerstein and Dr. Israel Zilbermann) – graduated 2013
4. Mrs. Karina Shemesh (co-supervisor Prof. Dan Meyerstein) – graduated 2018
5. Mr. Lerner Nadav (co-supervisor Prof. Dan Meyerstein) – graduated 2018

Since 2005: Supervising over20 students towards practical engineering diploma at the Technological College, Beer- Sheva, Israel

(b) Teaching:

2011-present – Instrumental Chemistry course for 3rd year chemistry students at Ben Gurion University

2011-2014 – General Chemistry B course for 1st year Life Science and Geology students at Ben Gurion University

• **Grants:**

Principle Investigator in following researches:

1998-2004: Transition metals as catalytic reagents in radiation induced damage (I. Zilbermann, E. Maimon, H. Cohen, D. Meyerstein) - Planning and Budgeting Committee of the Council for Higher education in Israel and Israel Atomic Energy Commission - $150,000

2004-2009: Reaction of radicals in solids and concentrated solutions (I. Zilbermann, E. Maimon, H.Cohen, D. Meyerstein) - Planning and Budgeting Committee of the Council for Higher education in Israel and Israel Atomic Energy Commission, $150,000

2004-2009: Novel anion exchangers for the selective extraction of uranium and the redox properties of the latter versus the lanthanide analogues (I. Zilbermann, E. Maimon, H. Cohen, D. Meyerstein) - Planning and Budgeting Committee of the Council for Higher education in Israel and Israel Atomic Energy Commission, $160,000

2009-2014: New redox – functionalized ligands for the selective determination of environmentally polluting ions. (E. Maimon, M. Gozin) - Planning and Budgeting Committee of the Council for Higher education in Israel and The Israeli Atomic Energy Commission - $150,000

2010-2015: Basic Inorganic Chemistry of actinides, lanthanides and transition metal complexes (I. Zilbermann, E. Maimon – NRCN; R. Caciuffo-ITU, Germany) - JRC European Consortium, $250,000

2015-2019: Kinetics and mechanisms of the reactions of secondary radicals with transition metal complex's: Implications for their biological activity. (E. Maimon, S. Goldstein) - Israel Atomic Energy Commission - $350,000

• **Synopsis of research**

1. Synthesis of metallo-cyclam and cyclam-like complexes

The synthesis of aza-macrocyclic compounds received considerable attention because of their relationship to biomimetic and catalytic systems and the applications of this type of chelating agents to biology and medicine. They have applications in modern chemical techniques such as magnetic resonance imaging, imaging with radioisotopes and radiotherapy, i.e. techniques where metal complexes with extreme kinetic and thermodynamic stability toward metal release are required. There has been a particular interest in the preparation and characterization of coordination compounds with aza-macrocyclic ligands with pendant substituents for the reasons given above. The complexation properties of polyaza-macrocycles are governed mainly by the macrocyclic ring size.

N-Functionalization of these macrocycles may enhance their metal-ion selectivity and the stability of metal complexes depending on the coordination properties of the pendant arms. The systems considered in my research are essentially restricted to macrocyclic or polydentate ligands (most of them saturated) preferentially containing nitrogen atoms and pendant arms. An important characteristic of aza-macrocyclic compounds is the existence of multiple equilibria between species in solution. Indeed, aza-macrocyclic ligands with a saturated framework are basic compounds which undergo multiple N-aza protonation reactions. Introduction of pendant groups (N-pendant) in the ligand, e.g. NR, $NRCOO^-$, $NRCONH_2$, etc., loses or adds one additional site that might be protonated. Interactions via nitrogen atoms with the media would be lost depending on the number of the protonable N-pendant groups introduced. The presence of this kind of pendant groups also induces additional inter- and intramolecular equilibria exchanges, intramolecular bonds, coordination ability and selectivity for ionic monoatomic species, stereochemical, structural and conformational exchanges in the complexes among others changes. We studied several such systems mainly based on cyclams and cyclam like ligands. Most of the complexes studied contained Ni(II)[6,8,9,13,14,15,17,18,20,27,29,31,35,36], Cu(II)[3,4,19,29] but also Co(II)[28]; Ce(III)[23] and Rh(III)[25]. We synthesized all the complexes either by multi-step synthesis (the ligand first) or by one pot template synthesis. The ligands and/or the complexes were characterized by elemental analysis, NMR, MS, ESI-MS, IR and UV-vis techniques. The nature of the pendant arms substituted on the ligating nitrogens stabilized thermodynamically either low valent species(Ni(I);Cu(I); Co(I)) in the case of loss of hydrogen bonds or high valent species in the case of extended hydrogen bonds(Ni(III); Cu(III); Ce(IV)) or further ligation provided by hydrophilic charged pendant arms(Ni(III)).

2. Analytical characterization and study of redox properties of transition metal complexes in aqueous solutions

The complexation properties of polyaza-macrocycles are governed mainly by the macrocyclic ring size. *N*-Functionalization of these macrocycles may enhance their metal-ion selectivity and the stability of metal complexes depending on the coordination properties of the pendant arms. The systems studied by me are essentially restricted to macrocyclic or polydentate ligands preferentially containing nitrogen atoms and pendant arms. Properties of the compounds considered were mainly restricted to UV–vis, NMR, ESR and IR spectroscopy, electrochemical and chemical characterizations of the systems and reactions with oxidizing/reducing radical species produced mainly by radiation chemistry techniques as well as electro-activation of small molecules, i.e. O_2 and NO. Fast kinetics were measured using pulse radiolysis and stopped flow techniques.

Some examples will be emphasized below:

a. Qualitative studies based on molecular models described the five possible conformational isomers (trans-I-trans-IV, cis V) of planar complexes of the "classic" macrocyclic ligand system, cyclam. Of the five possible configurational isomers of $[Ni(cyclam)]^{2+}$, it has long been supposed that the transIII configuration is the most stable one.
The isomerization of the macrocyclic frame bound to the nickel ion both in the +1 and +3 oxidation states of the metal was also reported. Isomerization leads to an equilibrated mixture of a ca. 1:3 ratio (trans I: trans III) in aqueous solutions over a period of several hours. The isomerization process could in principle proceed via one of the following mechanisms: a) deprotonation of one of the coordinated amino groups followed by inversion; b) cleavage of the Ni–N bond followed by inversion. In order to differentiate between these mechanisms, it was decided to see whether the isomerization is accompanied by proton exchange of the N–H groups with the solvent. For this purpose ^{1}H-NMR experiments were carried out in order to see whether the N–H groups are transformed into N–D groups when the oxidation reaction is carried out in D_2O. This study used the pulse radiolysis technique as well in order to characterize (UV-vis detection) the transients involved in the isomerisation processes. The following conclusions were derived:

i. Detachment of the Ni–N bond and inversion presumably via the cis-V isomer. This mechanism is relevant to low valent nickel complexes [13,14] and seems to occur in general for tetramethyl alkylated cyclam complexes as was also observed for copper [4].
ii. Deprotonation of coordinated N–H and inversion, presumably also via the cis-V isomer. This mechanism seems to be relevant to high oxidation state complexes. This mechanism explains the reason for a faster isomerization step in the case of nickel for the tervalent complex vs. the divalent complex. [13,14]

b. We and others have shown that nickel(II) complexes, with macrocyclic ligands, are reduced reversibly to relatively stable nickel(I) species inaqueous solution.[14] The redox potentials and lifetimes of the Ni(I) complexes are affected mainly by three factors: 1) substitution on the macrocyclic ring (especially on the nitrogens); 2) ring size and 3) saturation of the macrocyclic ring. Thermodynamic and/or kinetic stabilization of the monovalent nickel complexes is achieved by N-alkylation of the macrocyclic ligands.[14] As such we decided to study the effect of the redox potential, and plausibly of steric hindrance, of the cyclam and cyclam substituted nickel complexes on the rate of dehalogenation and on the detailed mechanism of the process us. The C-substituted and the N-substituted tetraazamacrocyclic ligands were chosen as they affect both the redox potential of the central cation and impose different steric strains on the complex and on the approach of the substrate to the central nickel cation.

Using electrochemistry and pulse radiolysis we elucidated the mechanism of the electrocatalytic debromination processes with the studied complexes. The rate of the debromination to yield bromide and the dehalogenated complex depends mainly on the redox potential of the $Ni^{II/I}$ couple increasing with the free energy gain in the reaction. We proposed that studied nickel complexes may be bound to modified electrodes, and might be useful as electrocatalysts for the dehalogenation of aliphatic halo-organic compounds.[8] Surprisingly using pulse radiolysis in the very same study we have shown that formate radical dehalogenates $(CH_2Br)_2C(CH_2OH)_2$ in a radical-induced catalytic process, i.e. formate acts via a hydrogen-atom-transfer mechanism. This process was studied in detail in a subsequent work[10].

c. Ni(II) and Co(II) complexes, with suitable macrocyclic ligands, are reduced reversibly to relatively stable nickel(I) and cobalt(I)species, respectively, in aqueous solutions. Nickel(I) macrocyclic complexes have attracted considerable attention because they enable the electrocatalytic reduction of alkyl halides, see above.

Cobalt(I) complexes are used in catalytic reductions including those analogous to B_{12}.

As such in one of our studies we decided to study the mechanisms ofreduction of maleate and fumarate by Ni(I)cyclam using the pulse radiolysis technique. The results differ significantly from one substrate the other in spite of their similarity. The difference is was shown to be mainly due to thefact that the radical anions formed in the reduction of both substrates have differentcharacteristics due to the strength of the hydrogen bond in the radical anion of the maleic acid. The reactions observed areattributed to the equilibrium reactions between the radiolytically produced Ni(I) species and maleate or fumarate in the solution which produced Ni-alkene (d-π) complexes in analogy to a previously studied Ni(I)-ethylene system[27].

In a subsequent study we decided to investigate whether the reduction of alkenes is a general reaction of low valent tetra-aza transition metal complexes. In this study, the reactions of substituted cyclam complexes of Co(II) with maleate were investigated by pulse radiolysis. The mechanism observed in the Co-maleate systems is similar to that observed inthe nickel system [27] in that initially maleate forms a d-π complex with the central metal cation. It differs from that observed for the nickel system in that the yield of succinate (main product) is considerably lower in the cobalt system. This is expected

due to the differences in redoxpotentials of the M(II/I) couples of the studied complexes.The results point out that the monovalent complexes investigated, formed by thepulse radiolysis method or by γ radiation, react with maleate to form the complex M(I)-maleate (M=Ni or Co) in an equilibrium reaction. From this intermediate, there are different pathways and different end productsdepending on the central metal cation and the different ligands of the complexes. The Co(I) complex reduces less maleate than the Ni(I) complexes as several side reactionsoccur producing molecular hydrogen.[28]

d. Tetraazamacrocyclic transition metal complexes were shown to activate chemically or electrochemically small molecules of general interest (biologically, industrially, environmentally) like NO, O_2, CO_2 etc.

The role of NO in a variety of physiological processes renders its reaction mechanisms with species present in biological media of importance. Of special interest are nitrosation processes that are involved in signalling and pathologicalprocesses as well as in buffering the concentration of NO in the cell.

It is well known that Ni(III)L, L = 1,4,8,11-tetraazacyclotetra-decane complexes are stabilized by axially bound pendant primary amine groups, which are covalently linked to the macrocyclic frame . However, we have shown that Ni(III)(cyclam), $Ni^{III}L$, oxidizes methyl amine via a radical mechanism involving an intermediate with a radical on methyl amine nitrogen [9]. As NO is a radical as well and may induce either nitrosation or bind to Ni(III) and reduce it, we decided to check the mechanism of reaction. The results obtained by using stopped flow to follow up the kinetics and performing product analysis by ^{13}C NMR and ESI-MS showed that the mechanism involved is the following:

Reaction of NO with the ligand bound to the central cation(Ni^{III}), the former having a lone electron pair situated on the atom ligated to the cation. This process often requires proton loss to form the lone pair[17]. Reactions of this type were previously attributed to attack of NO on the lone pair followed by electron transfer. This very mechanism was confirmed by a later study of ours to be more general for nitrosation of peptides by Ni^{III}glyglygly; Cu^{III}glyglygly; Fe^{III}glyglygly and their alaglygly analogues. The rate constants were found to be dependent on the redox potentials of the $M^{III/II}$[20].

In a different study we have looked at the interaction of a non saturated tetraazamacrocycle complex namely Ag(II) tetraphenylsulfonateporphyrin with NO[4].

The silver complex was electrochemically precipitated on glassy carbon and gold electrodes. Electrochemical quartz crystal microbalance (EQCM) results indicated the formation of an Ag(II)–Ag(III) porphyrin dimer species. The films thus formed catalyze NO reduction at relatively high-reduction potentials (E < 0.4 V vs. SCE). The electrochemical results seem to indicate that the catalytic cycle in the case of NO involves formation of Ag(II)TPPS– Ag(II)TPPS(NO^+) and its electroreduction to regenerate Ag(II)TPPS–Ag(III)TPPS and NO-reduction products. The films also showed catalytic behaviour toward O_2 reduction at relatively low potentials (E <-0:1 V vs. SCE)[4].

3. Design of electron-exchange columns

In recent years functionalized silica and sol–gel-silica have attracted considerable interest due to their high porosity, matrix rigidity and the versatility of the functional groups that can be attached to and/or entrapped in the matrix. Therefore they serve as key materials in various fields such as catalysis, optics, electrochemistry, separation and biology. Many of these applications require binding of a transitionmetal complex to the functional groups. Therefore, in these cases, the functional group has to contain a good chelating ligand. Poly-azamacrocyclic ligands, especially cyclam (1,4,8,11-tetraazacyclotetradecane), form very stable complexes with many transition-metal ionsand stabilize complexes with uncommon oxidation states [3,4,6,8,9,13,14,17-19,23,27-29,36]. In principle the ligand, or the complex, can be immobilized onto a sol–gel matrix either by entrapmentor by covalent binding.The entrapment of a macrocyclic ligand often occurs in pores that sterically hinder the binding of the metal cation in the plane of the ligand. Entrapment of the ligand and/or the complex is often accompanied by slow loss of the entrapped species by elution. Therefore covalent binding is preferred. In principle entrapment of a strong reversible redox reagent in a stable sol–gel matrix would yield an optimal electron exchange column. Such columns will react by oxidizing or reducing a desired substrate operating in a mode analogous to ion exchange columns. Recently, we have shown that nickel-complexes with tetraazamacrocyclic ligands (nickel-cyclamnickel-trans-III-meso-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane;nickel-1-propyl-1,3,5,8,12-pentaazacyclotetradecane) may be entrapped in silica-sol–gel matrices by the biphasic method, i.e. noncovalent entrapment of the complex in the matrix. Electron exchange columns from these materials were shown to operate with relative high efficiency via the $Ni^{3+/2+}$ redox couple[31;35].

4. Synthesis and characterization of biorelevant molecules with medical use

There is a growing interest in developing simple and accurate techniques for the determination of the antioxidant properties of biological samples,especially of blood, as it reflects different oxidative stresses in the body. It was found that stable nitroxide radicals (NRs) are reduced by blood and some other biological materials, to the corresponding hydroxylamines. This reduction process can be followed by EPR spectroscopy. The kinetics of the nitroxides disappearance, thus measured, provide useful biochemical and biophysical information about the antioxidant properties of biological systems. Most NRs are reduced by ascorbate and not by other biological antioxidants. Therefore, NRs were used as models of persistent radicals to study the antioxidant function of ascorbate in human erythrocytes.

In one of my studies in collaboration with physicians colleagues [7], I synthesized the metastable nitroxide radical: $R^{\cdot}$ = 5-dimethylaminonaphthalene-1-sulfonyl-4-amino-2,2,6,6-tetramethyl-1-piperidine-oxyl. The kinetics of reduction of the radical $R^{\cdot}$ by blood and its components were studied using the EPR technique. The results demonstrate that $R^{\cdot}$ is adsorbed to the outer surface of the membrane and does not

penetrate into the erythrocytes. A series of control experiments in PBS demonstrate that ascorbate is the only natural reducing agent that reacts with $R^{\cdot}$. The results demonstrate that:

a. The erythrocytes catalyze the reduction of $R^{\cdot}$ by ascorbate.

b. The rate of reduction of the radical is high though it does not penetrate the cells.

c. In human erythrocytes there is an efficient electron transfer route through the cell membrane.

d. The study points out that $R^{\cdot}$ is a suitable spin label for measuring the reduction kinetics and antioxidant capacity in blood as expressed by reduction by ascorbate[7].

Another study performed by me in collaboration with physicians and nuclear physicists, this time during my sabbatical at Maryland University, regarded the synthesis and use of a drug to be used for prostate cancer therapy[37].

According to the American Cancer Society, prostate canceris the most frequently diagnosed cancer and the secondleading cause of cancer death in men. Because of this, thedevelopment of new therapy options involving targeteddrug delivery to improve the efficacy of prostate cancertreatment is essential and has recently gained momentumin the field of boron neutron capture therapy (BNCT). BNCT is abinary radiation cancer treatment with potentially significanttherapeutic advantages compared to conventionalchemical and radiation therapies. The treatment is basedon specific cell killing by neutron irradiation of cancercells that have been preferentially loaded with ^{10}B.The reaction between a thermal neutron and ^{10}B produces high-linear energy transfer (LET) α particles and ^{7}Li nuclei with high probability because of the large thermal neutron absorption cross section of ^{10}B. These high-LET particles impart their energies within a 9 μm range. Because this distance is on the same scale as atypical cell diameter, the particles are theoretically capable offatally damaging cells containing the ^{10}B while leaving neighboring cells unharmed. The aim of targeted drug therapy is to selectively deliver drugs to cancer cells while minimizing uptake in surroundingnormal cells. In recent years, a number of promising BNCT agents have been developed to improve biodistribution through synthetic chemical and biochemical-biophysical strategies. Amongst the broad range of targeting strategies, liposome-based delivery of hydrophilic and hydrophobic boron-containingcompounds has provided promising results.

The cholesteryl ester of carborane (BCH), a boron-containing cholesteryl ester was synthesized by me and its efficacy as a boron neutron capture therapy (BNCT) agent for the targeted irradiation of PC-3 human prostate cancercells was examined. The results showed that BCH delivery by means of encapsulation in a lipid bilayer resulted in a relative high boron uptake with minimal cytotoxic effects. PC-3 cells treated with BCH and exposed to a thermal neutron fluence yielded a 20 – 25% decrease in clonogenic

capacity. The decreased survival is attributed to the generation of high-LET α particles and ^{7}Li nuclei that deposit energy in densely ionizing radiation tracks.

The main conclusion was that liposome-based delivery of BCH is capable of introducing sufficient boron to PC-3 cells for BNCT. High-LET α particles and ^{7}Li nuclei generated from ^{10}B thermal neutron capture significantly decrease colony formation ability in the targeted PC-3 cells[37].

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